Practice Guidelines for the Control and Management of Tuberculosis

Ministry of Health Malaysia

Academy of Medicine of Malaysia
# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of contents</td>
<td>iii</td>
</tr>
<tr>
<td>Foreword</td>
<td>vii</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>viii</td>
</tr>
<tr>
<td>List of committee members</td>
<td>ix</td>
</tr>
<tr>
<td>1. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>2. Epidemiology</td>
<td>2</td>
</tr>
<tr>
<td>3. Diagnosis of Tuberculosis</td>
<td>3</td>
</tr>
<tr>
<td>3.1 Pulmonary Tuberculosis</td>
<td>3</td>
</tr>
<tr>
<td>3.2 Extra pulmonary Tuberculosis</td>
<td>5</td>
</tr>
<tr>
<td>3.3 Screening of high risk groups</td>
<td>6</td>
</tr>
<tr>
<td>3.4 Notification of Tuberculosis</td>
<td>7</td>
</tr>
<tr>
<td>3.5 Tuberculosis Classification</td>
<td>7</td>
</tr>
<tr>
<td>3.6 Definition of terms</td>
<td>9</td>
</tr>
<tr>
<td>3.7 Radiological Classification</td>
<td>10</td>
</tr>
<tr>
<td>4. Treatment of Tuberculosis</td>
<td>12</td>
</tr>
<tr>
<td>4.1 Treatment categories</td>
<td>12</td>
</tr>
<tr>
<td>4.2 Chemotherapy</td>
<td>12</td>
</tr>
<tr>
<td>4.2.1 Drugs</td>
<td>13</td>
</tr>
<tr>
<td>4.2.2 Treatment regimens</td>
<td>13</td>
</tr>
<tr>
<td>4.2.3 Anti-tuberculosis drugs &amp; the recommended doses</td>
<td>15</td>
</tr>
<tr>
<td>4.2.4 Flow chart for recommended treatment regime</td>
<td>16</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>5. Patient monitoring</td>
<td>17</td>
</tr>
<tr>
<td>5.1 Treatment response</td>
<td></td>
</tr>
<tr>
<td>5.2 Patient compliance</td>
<td></td>
</tr>
<tr>
<td>6. Drug toxicity monitoring and management</td>
<td>19</td>
</tr>
<tr>
<td>6.1 Monitoring for drug toxicity</td>
<td></td>
</tr>
<tr>
<td>6.2 Management of drug toxicity</td>
<td></td>
</tr>
<tr>
<td>7. Management of tuberculosis in special situations</td>
<td>23</td>
</tr>
<tr>
<td>7.1 Tuberculosis in children</td>
<td>23</td>
</tr>
<tr>
<td>7.2 Tuberculosis during pregnancy &amp; lactation</td>
<td>25</td>
</tr>
<tr>
<td>7.3 Tuberculosis treatment for women taking OCP</td>
<td>26</td>
</tr>
<tr>
<td>7.4 Tuberculosis in patients with liver impairment</td>
<td>26</td>
</tr>
<tr>
<td>7.5 Tuberculosis in patients with renal impairment</td>
<td>27</td>
</tr>
<tr>
<td>7.6 Extra pulmonary tuberculosis</td>
<td>27</td>
</tr>
<tr>
<td>7.7 Tuberculosis in patients with HIV infection</td>
<td>27</td>
</tr>
<tr>
<td>8. Fixed-dose combinations (FDC) of anti-tuberculosis drugs</td>
<td>29</td>
</tr>
<tr>
<td>8.1 Advantages</td>
<td></td>
</tr>
<tr>
<td>8.2 Disadvantages</td>
<td></td>
</tr>
<tr>
<td>9. DOTS—Directly Observed Treatment, short-course</td>
<td>31</td>
</tr>
<tr>
<td>9.1 Advantages of DOTS</td>
<td></td>
</tr>
<tr>
<td>9.2 DOTS in Malaysia</td>
<td>32</td>
</tr>
<tr>
<td>10. Defaulter tracing and retrieval</td>
<td>33</td>
</tr>
<tr>
<td>10.1 Definition of defaulter</td>
<td></td>
</tr>
<tr>
<td>10.2 Contact management</td>
<td></td>
</tr>
<tr>
<td>11. Outcome analysis</td>
<td>34</td>
</tr>
</tbody>
</table>
12. Management of Resistant Tuberculosis
   12.1 Definition
   12.2 Management of resistant tuberculosis
      12.2.1 Pharmacological treatment
   12.3 BCG vaccination in Malaysia
   12.4 Tuberculosis in foreign workers
   12.5 Chemo prophylaxis

13. Prevention of Tuberculosis among Health Care Workers (HCW)

References

Appendix
Foreword

The World Health Organization (WHO) has acknowledged the fact that Tuberculosis (TB) is re-emerging in many parts of the world with a vengeance. This led to WHO declaring TB as a global emergency in 1993. Amongst others, the HIV pandemic as well as global complacency and neglect towards the disease were identified as the principal factors causing the resurgence.

Although the situation in Malaysia is not as alarming as in many other parts of the world, the latest statistics appear to show that TB as a health problem is on the increase. HIV infected population afflicted with TB is increasing and they form the major killer among this population group.

Therefore it is timely that our doctors are armed with the latest knowledge and strategies to combat this scourge. This booklet, prepared by doctors and paramedics from the Ministry of Health and the Universities is to fulfill this aim. In particular, it is hoped that with the effective implementation of the DOTS strategy and application, TB as a health problem would be greatly reduced, if not eliminated in the not too distant future.

This booklet will certainly be of benefit to all primary care doctors and also everyone else who manages patients with TB.

I also wish to congratulate the committee for coming out with this valuable booklet.

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<th>Name</th>
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<td>Dr Jeffrey Abu Hassan</td>
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<td>Dr Fariza Mohd Yusof</td>
</tr>
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<td>23</td>
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</tbody>
</table>
1. Introduction

Tuberculosis (TB) as a health problem has been with us from time immemorial. Ever since the early 50's, the Malaysian Government has realised its magnitude in terms of human suffering and mortality. Hence enormous resources were injected, in terms of finance and manpower to achieve a situation where it became no longer a public health problem. However, in recent years tuberculosis has re-emerged as a major threat in terms of morbidity and mortality globally. More recent statistics testify that tuberculosis cases are either on the rise or stagnating.

Today, 50 years after the introduction of chemotherapy for tuberculosis, there are still eight million new infectious cases detected all over the world. *Mycobacterium tuberculosis* probably kills more adults (three million) each year than any other single infectious pathogen1. Since tuberculosis primarily affects those in their most productive years, the socio-economic implications of the disease are tremendous. The main reasons for this are attributed to the following:

(i) The rising incidence of HIV/AIDS worldwide and the close interaction between tuberculosis and HIV/AIDS.

(ii) Increasing international migration.

(iii) The emergence of multi-drug resistant tuberculosis (MDR TB).

(iv) Economic strife, war, famine and natural disasters which disrupted existing Tuberculosis Control Programmes.

(v) Decreased awareness about tuberculosis amongst medical personnel including doctors.

(vi) The low priority given to tuberculosis control in terms of resource allocation and training.

(vii) Changes in global population demography.

In Malaysia over the past 10 years there has been a steady increase in yearly notification of new cases of tuberculosis (infectious cases and all forms).2
2. Epidemiology

*Mycobacterium tuberculosis* infects a third of the world’s population. There were eight million new cases per year (1995)\(^2\). Ninety-five percent of tuberculosis cases and 98% of tuberculosis deaths are in developing countries. Seventy-five percent of tuberculosis cases in developing countries are in the economically productive age group (15-50 years). Since the early 1990s most countries have reported either increased notification or stagnation in number of cases.

In Malaysia for the year 1999, 14908 new cases of tuberculosis were reported. Majority of the cases were in the 15-50 years age group. There were 603 cases of HIV and tuberculosis co-infections notified for the same year. The total number of deaths due to tuberculosis reported was 853. This makes tuberculosis the single most important killer amongst notifiable infectious diseases in Malaysia.
3. Diagnosis of Tuberculosis

Diagnosis of tuberculosis is based on clinical, radiological and/or bacteriological evidence.

3.1 Pulmonary tuberculosis

The commonest form of tuberculosis in adults is post-primary pulmonary tuberculosis. It is the only form of tuberculosis which is infectious and thus has great epidemiological significance.

3.1.1 Symptoms & Signs

Symptoms which suggest pulmonary tuberculosis include:
- Cough persisting for more than two weeks
- Cough with sputum which is occasionally bloodstained
- Loss of appetite and loss of weight
- Fever
- Dyspnoea, night sweats, chest pain and hoarseness of voice, all of which are not common

Patients with the above symptoms should be screened for tuberculosis.

Signs can be subtle especially in minimal cases, or may be obvious including those of consolidation, fibrosis or stony dullness caused by pleural effusion.

3.1.2 Investigations

The laboratory investigations include sputum direct smears for acid-fast bacilli, which are usually positive in cavitary disease. Three specimens, preferably including one early morning specimen, should be collected for diagnosis. Culture using egg-based media takes
up to 8 weeks for a final result. There are radiometric methods such as the BACTEC, which can give results within 2 weeks. These can be used when there is a need for early diagnosis and in smear-negative cases. Sensitivity tests using radiometric methods, which yield equally rapid results, can be performed in situations where drug resistance is suspected and urgent results are required. Specimens obtained via bronchoscopy can be used for the above tests.

Chest x-rays often reveal lesions in the apical and posterior segments of the upper lobes. Lesions are often soft in active pulmonary tuberculosis and there is usually little or no fibrosis or calcification. These latter findings would suggest healed tuberculosis. Cavities suggest the diagnosis of active disease unless the patient has been previously treated. Apart from the typical sites at the apices, other sites such as the apical segment of the lower lobes may also be involved.

The tuberculin or Mantoux test has some role in the diagnosis of tuberculosis especially in pediatric cases and cases of extra pulmonary tuberculosis. The Mantoux test is carried out in government hospitals in Malaysia using 2 tuberculin units (T.U.) in 0.1 ml of prepared solution. The result is read after 72 hours. A diameter of indurations of less than 10mm is graded as negative but this does not exclude a diagnosis of tuberculosis. A reading of 10mm or more in a child or adult is considered positive. A diameter of 15mm or more in a child is considered significant and may indicate recent infection. A positive Mantoux test merely indicates tuberculosis infection and not necessarily active disease.

The erythrocyte sedimentation rate (ESR) has little role and cannot be recommended for routine use in the diagnosis and follow-up of patients with tuberculosis.
Recently developed diagnostic tests utilizing nucleic acid amplification by polymerase chain reaction (PCR) can give rapid results but are expensive. Since these tests can detect small numbers of organisms, false-positive reactions may result from cross-contamination in busy clinical laboratories; false-negatives may result from the presence of inhibitors or lack of target gene sequences in the causative strain. However, it must be remembered that PCR can give a positive result in patients who are already on anti-tuberculosis treatment who are excreting small number of non-viable bacilli, thus this test is not of value for follow-up of patients on treatment.³

The value of serological tests for tuberculosis should be studied in various operational situations before they are widely applied. Newer serodiagnostic tests using purified antigens have good specificity but lower sensitivity than culture for tubercle bacilli.⁴

3.2 Extra pulmonary Tuberculosis

This is mainly due to lympho-haematogenous dissemination during primary tuberculosis infection.

Symptoms are often non-specific, including lassitude, anorexia, fever and weight loss. The specific features relate to the organ involved.

*Tuberculous lymphadenitis* can be diagnosed by fine needle aspiration (FNA) of glands which are accessible especially in the neck. The specimen should be sent for direct smear, culture for tubercle bacilli and cytological examination. Biopsy may be needed in cases in where results from fine needle aspiration are negative.

*Tuberculous pleural effusion* is diagnosed from pleurocentesis and pleural biopsy. The pleural aspirate
often reveals straw-coloured fluid with protein > 30 g/l, low glucose (< 30 mg/dl), and with cells (mainly lymphocytes). Direct smears and cultures of the pleural fluid should be requested for.

The diagnosis of **genito-urinary tuberculosis** can be made from radiological investigations (IVU) and culture of urine for *Mycobacterium tuberculosis*. **Genital tuberculosis** requires tissue biopsy for confirmation.

**Tuberculosis of bones and joints** is often diagnosed from x-rays and tissue biopsy. The diagnosis of tuberculosis of intestines and peritoneum would require tissue biopsy and barium studies. Diagnosis of **cutaneous tuberculosis** may be made by skin biopsy.

**Miliary tuberculosis** is often diagnosed on plain chest x-ray although liver biopsy is sometimes done and may reveal granulomas in up to 88% of the cases. Diagnosis of **tuberculous meningitis** requires cerebrospinal fluid for microscopic, biochemical and bacteriological examination; however the patient is often ill and there is a role for a therapeutic trial of anti-tuberculosis treatment in these cases. CT scans of brain can help by showing features of basal meningitis, tuberculoma or obstructive hydrocephalus.

### 3.3 Screening of high risk groups

The following constitute high-risk groups which should be screened for active tuberculosis:

(i) Contacts of sputum positive tuberculosis cases.

(ii) Persons with HIV infection.

(iii) Immigrants from countries with high tuberculosis prevalence.

(iv) Persons in institutions such as prisons and drug rehabilitation centers.

(v) Persons with other medical risk factors such as diabetes mellitus, silicosis, renal failure, those on prolonged corticosteroid or other immunosuppressive therapy and haematological malignancies.
3.4 Notification of Tuberculosis

All confirmed tuberculosis cases (bacteriological and/or radiological and /or clinical) must be notified to the nearest District Health Office using "Borang Notis" within 1 week of diagnosis. This is required under the Infectious Diseases Act 342, 1988.

3.5 Tuberculosis Classification

The following is a suggested system for classification of cases of tuberculosis (adapted from WHO treatment guidelines).⁸

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary tuberculosis</td>
</tr>
<tr>
<td>Pulmonary tuberculosis, smear-positive</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Pulmonary tuberculosis, smear-negative</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>(ii) Tuberculosis in a patient whose initial sputum smears were negative, who had sputum sent for culture initially, and whose subsequent sputum culture result is positive for <em>M. tuberculosis</em>.</td>
</tr>
<tr>
<td>Extra pulmonary tuberculosis</td>
</tr>
<tr>
<td>Pulmonary with Extra pulmonary tuberculosis</td>
</tr>
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</table>

SOURCE: WHO TREATMENT GUIDELINES.
### 3.6 Definition of terms

<table>
<thead>
<tr>
<th>TERMS</th>
<th>Definition</th>
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<tbody>
<tr>
<td>New case</td>
<td>A patient who has never had treatment for tuberculosis or has taken anti-tuberculosis drugs for less than 4 weeks' duration in the past.</td>
</tr>
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</table>
| Relapse case      | (i) **Sputum positive relapse**  
A patient who has been declared cured of any form of tuberculosis in the past by a doctor, after one full course of chemotherapy, and has become sputum smear-positive.  

(ii) **Sputum negative relapse**  
A patient who has been declared cured of any form of tuberculosis in the past by a doctor, after one full course of chemotherapy, and has developed active disease based on bacteriological, histological or clinical and radiological assessment. |
| Chronic case      | A patient who remained or becomes smear-positive again after completing a fully supervised re-treatment regimen. |
| Treatment failure | A patient who, while on treatment, remained or became again smear-positive 5 months or later after commencing treatment. It is also a patient who was initially smear-negative before starting |
treatment and became smear-positive after the second month of treatment.

**Treatment after interruption**

A patient who interrupts anti-tuberculosis treatment for 2 months or more, and then returns to the health service with smear-positive sputum.

(Sometimes smear-negative but still with active tuberculosis as judged on clinical and radiological assessment).

**Transferred in case**

A patient transferred from another centre for continuation of treatment of tuberculosis. A transfer implies that the center to which the patient is transferred undertakes the responsibility of continuing to treat the patient and supervising progress. A patient is not considered to have been transferred if he/she presents at another treatment centre merely to obtain treatment.

### 3.7 Radiological classification

Classification of radiological extent of disease in the initial chest x-ray for cases of pulmonary tuberculosis may be standardized using the following criteria:

<table>
<thead>
<tr>
<th><strong>RADIOLOGICAL CLASSIFICATION</strong></th>
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<tbody>
<tr>
<td><strong>Minimal</strong></td>
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<tr>
<td>Slight lesions without demonstrable cavitations confined to a small part of one or both lungs. The total extent</td>
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</table>
of the lesions should not exceed the volume of lung on one side which lies above the second chondrosternal junction and the spine of the fourth or the body of the fifth thoracic vertebra.

**Moderately advanced**

One or both lungs may be involved but the total extent of the lesions should not exceed the following limits:

(i) Disseminated lesions of slight to moderate density not exceeding the total volume of one lung or the equivalent in both lungs.

(ii) Dense and confluent lesions not exceeding one third the volume of one lung.

(iii) Total diameter of cavitations, if present, must be less than 4 cm.

**Far advanced**

Lesions are more extensive than moderately advanced.

For extra pulmonary tuberculosis involvement of an anatomical site results in classification as severe disease if there is either a significant acute threat to life (e.g. pericardial tuberculosis) or risk of subsequent severe handicap (e.g. spinal tuberculosis) or both (e.g. meningeal tuberculosis). The following forms of extra pulmonary tuberculosis are classified as severe: meningitis, miliary, pericarditis, peritonitis, bilateral or extensive pleural effusion, spinal, intestinal, genito-urinary. The following forms of extra pulmonary tuberculosis are classified as less severe: lymph node, pleural effusion (unilateral), bone (excluding spine), peripheral joint, skin.
4. Treatment of Tuberculosis

4.1 Treatment categories (modified from WHO)\(^6\)

*Treatment categories*

- **Category I**
  - New case

- **Category II**
  - Relapse
  - Treatment Failure
  - Treatment after Interruption

- **Category III**
  - Chronic Case

4.2 Chemotherapy

Modern chemotherapy should cure almost all newly diagnosed patients if an effective regimen is prescribed for an adequate period of time and if the patient ingests the prescribed medications regularly. A six months course of chemotherapy has proven highly effective and reliable.\(^8\)\(^,\)\(^9\)

**The aims of treatment are:**...

(i) To reduce morbidity  
(ii) To prevent mortality  
(iii) To prevent relapse of tuberculosis  
(iv) To decrease transmission  
(v) To prevent the emergence of MDR TB
4.2.1 Drugs

Five drugs are considered essential (1st line) for the treatment of tuberculosis. These are isoniazid (H), rifampicin (R), pyrazinamide (Z), streptomycin (S)

* Isoniazid (H),
* Rifampicin (R),
* Pyrazinamide (Z), Essential 1st line drugs
* Streptomycin (S) &
* Ethambutol (E).

4.2.2 Treatment regimens

Treatment regimens are divided into:

(i) Initial or intensive phase

(ii) Continuation or maintenance phase.

During the intensive phase, three or four drugs are given daily. This leads to rapid sputum conversion and amelioration of clinical symptoms. During the continuation phase, two or three drugs are usually given intermittently. The sterilizing effect of the therapy eliminates remaining bacilli and reduces drastically the chances of subsequent relapse.
(i) Intensive phase: 2SHRZ or 2EHRZ or 2HRZ (2 months of daily doses)

(ii) Continuation phase: \(4H^2R^2\) or \(4S^2H^2R^2\) or \(4HR\) or \(4H^3R^3\) or \(4S^3H^3R^3\) (Duration may be extended for severe forms of extra pulmonary tuberculosis and immuno compromised patients).

* The number preceding the treatment regimen refers to the treatment duration in months.

** The subscript below the drug symbol refers to the frequency of doses per week.

(i) Send *Mycobacterium tuberculosis* culture and sensitivity (MTB C&S) (Rapid culture method if available)

(ii) Do not initiate standard therapy

(iii) Refer to chest physician or physician in charge of chest clinic

(iv) Subsequent drug regimen based on sensitivity results and clinical response.
(i) Send *Mycobacterium tuberculosis* culture and sensitivity (MTB C&S) (Rapid culture method if available)

(ii) Refer to chest physician or physician in charge of chest clinic.

4.2.3 **Anti-tuberculosis drugs and the recommended dosages**

4.2.3.1 **1st line anti-tuberculosis drugs**

<table>
<thead>
<tr>
<th>1st line drug</th>
<th>Daily dosage</th>
<th>Biweekly dosage</th>
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<tbody>
<tr>
<td></td>
<td>mg/kg</td>
<td>max (mg)</td>
</tr>
<tr>
<td>Isoniazid (H)</td>
<td>5 - 8</td>
<td>300</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>10 - 15</td>
<td>600</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>20 - 40</td>
<td>1500</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>15 - 25</td>
<td>1200</td>
</tr>
<tr>
<td>Streptomycin (S)</td>
<td>15 - 20</td>
<td>1000</td>
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*Note: For patients more than 65 years of age, the dose of streptomycin should not exceed 750mg*
4.2.4 Flow chart for recommended 24 weeks (w) / 6 months (m) treatment regimen (adult)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Duration</th>
<th>Regimen</th>
<th>Investigation</th>
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<tbody>
<tr>
<td>1.</td>
<td>0 w (0 m)</td>
<td>2SHRZ / 2EHRZ</td>
<td>Baseline investigation FBC, RFT, LFT, RBS, HIV, Sputum AFB D/S, culture</td>
</tr>
<tr>
<td>2.</td>
<td>8 w (2 m)</td>
<td>4SHR²</td>
<td>4HR²</td>
</tr>
<tr>
<td>3.</td>
<td>8 w (2 m)</td>
<td>Continue Rx</td>
<td>Continue Rx</td>
</tr>
<tr>
<td>4.</td>
<td>8 w (2 m)</td>
<td>Completion of Rx 24 w (6 m)</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>24 w (6 m)</td>
<td>* follow up</td>
<td></td>
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\[\begin{array}{llll}
E &=& Ethambutol & FBC = \text{Full blood count} & RBS = \text{random blood sugar} \\
H &=& Isoniazid & LFT = \text{Liver function test} & HIV = \text{anti-HIV antibody (for screening)} \\
R &=& Rifampicin & RFT = \text{Renal function test} \\
S &=& Streptomycin & D/S = \text{Direct smear} & MTB = \text{Mycobacterium tuberculosis} \\
Z &=& Pyrazinamide & Rx = \text{Treatment} & C&S = \text{culture and sensitivity test} \\
W &=& week & M &=& month \\
\end{array}\]

Note: (*) Recommended to be done where facilities are available
5. Patient monitoring

5.1 Treatment response

In order to monitor sputum conversion and treatment outcome it is recommended that all patients who are initially sputum smear-positive have repeat sputum smears performed at the end of the second month of treatment. To verify treatment success, additional sputum smears should be taken at the fourth month and at the end of therapy for the 6 month regimens. Sputum cultures should be obtained at the start of treatment. Sensitivity tests for all available drugs if possible should be performed for new patients still positive at the end of the intensive phase of treatment.

5.2 Patient compliance

Patient non-compliance is the main cause of treatment failure; those who do not take prescribed medications with sufficient regularity and duration to achieve cure are most likely to fail.

Historically, long term institutional care was employed to overcome patient non-compliance. In certain settings today, hospitalisation has been one of the critical elements in achieving nearly 100% patient compliance to the intensive phase. A very high treatment completion rate can be achieved by adequate patient education.

Indications for hospitalisation include:

(i) Gravely ill patients
(ii) Cases of acute disseminated tuberculosis
(iii) TB involving CNS, pericardium, adrenal and spine.
(iv) MDR TB
(v) Patients who default frequently or whose compliance is suspect.
(vi) Complications such as haemoptysis, pneumothorax and empyema.

(vii) Associated diseases such as uncontrolled diabetes and renal failure.

(viii) Severe side-effects such as severe skin reactions or jaundice.

(ix) Patients who need desensitisation to antituberculosis drugs.

(x) Social reasons eg. Homeless patients, patients with poor family support.

Directly observed treatment, short-course (DOTS) has been shown to be feasible and highly successful towards achieving the objective of a 95% cure rate.
6. Drug toxicity monitoring and management

6.1 Monitoring for drug toxicity

Where facilities are available, all patients should have baseline measurements of liver enzymes, serum bilirubin, serum creatinine, blood urea and a full blood count. Serum uric acid can also be measured if pyrazinamide is used and a baseline examination of visual acuity should be obtained for patients to be treated with ethambutol. The purpose of these baseline tests is to detect any abnormality that would necessitate modification of the treatment regimen. In addition, these baseline tests allow for comparison with later measurements in the event of an adverse reaction. Patients with pre-existing liver disease, or conditions such as alcoholism known to potentiate hepatotoxicity of tuberculosis drugs, and children with severe forms of tuberculosis should have regular monitoring of liver function especially during the first few months of therapy.

All patients should be monitored clinically for adverse reactions during the period of chemotherapy. They should be instructed to report symptoms possibly caused by adverse reactions to the medications they are receiving. Patients should be seen by a doctor at least two monthly during therapy and should be specifically asked about such symptoms. Routine laboratory monitoring for asymptomatic patients is not necessary. If symptoms suggesting drug toxicity occur, appropriate laboratory testing should be performed to confirm such toxicity.

6.2 Management of drug toxicity

Minor side effects, such as gastrointestinal intolerance, are best managed by reassurance and symptomatic treatment and the patient should be encouraged to continue
anti-tuberculosis treatment. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) provide symptomatic relief for pyrazinamide related arthralgia.

The most common serious drug toxicity seen with short course therapy is hepatitis. Patients who develop symptoms of liver dysfunction such as nausea, vomiting, anorexia and abdominal pain during therapy should have their treatment stopped immediately. Many patients with drug-induced hepatotoxicity may be successfully restarted on the same drugs, when liver function returns to normal. This is best done in a setting where liver function can be carefully monitored, hence patients with this problem should be sent to a referral centre for further management.

Patients who develop hypersensitivity reactions, such as rash, to the two most potent drugs i.e. isoniazid and rifampicin, may be desensitised if a suitable regimen cannot be provided with the other drugs which the patient can tolerate. This is done by careful administration of increasing doses of the drug under close supervision. Desensitisation should not be attempted for patients with HIV infection.

The development of the following conditions contraindicate the further use of the causative drug: thrombocytopenia, shock and/or renal failure due to rifampicin, visual impairment due to ethambutol and eight cranial nerve damage from streptomycin.

6.2.1 Challenge dose for hypersensitivity reactions

Generally 1/10 of the therapeutic dose is used on the first day. The initial dose will depend on the severity of the hypersensitivity reaction. Hence the day 1 challenge dose may need to be adjusted.

If rash occur after 1st challenge dose, do not proceed. Wait for reaction to subside and then go on to the next drug. Challenge should be done for one drug at a time.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Challenge dose (mg)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
</tr>
<tr>
<td>Isoniazid (INH)</td>
<td>50</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Rifampicin (RFP)</td>
<td>75</td>
<td>300</td>
<td>450</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>250</td>
<td>1000</td>
<td>2000</td>
</tr>
<tr>
<td>Ethambutol (ETM)</td>
<td>100</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Streptomycin (SM)</td>
<td>125</td>
<td>500</td>
<td>1000</td>
</tr>
</tbody>
</table>

6.2.2 Desensitisation

Desensitisation is only done if one is unable to devise a suitable regimen of treatment without the offending drugs. If an alternative and suitable drug combination is available it is not necessary to start desensitisation. Desensitisation is done by daily administration of increasing doses until the therapeutic dose is reached. During desensitisation it is necessary to cover the patient with at least two other drugs, which the patient can tolerate.

The initial dose depends on the severity of the hypersensitivity reaction. Generally begin with 1/10 - 1/100 of the therapeutic dose and then the dose are doubled each time.

6.2.3 Gastrointestinal upset

Treat symptomatically first, and if still not relieved, the offending drugs can be withdrawn.
6.2.4 Drug interactions

6.2.4.1 Isoniazid

Isoniazid tends to raise plasma concentrations of anti-epileptic drugs such as phenytoin and carbamazepine by inhibiting their metabolism in the liver. The absorption of isoniazid is impaired by aluminium hydroxide.

6.2.4.2 Rifampicin

Rifampicin induces liver enzymes, and may increase the dosage requirements of drugs metabolised in the liver. These include protease inhibitors, cyclosporin, corticosteroids, oral contraceptive pill, oral hypoglycaemic agents, oral anticoagulants, phenytoin, cimetidine, theophylline and digitalis glycosides.

Biliary excretion of radiocontrast media and Sulphobromophthalein sodium may be reduced and microbiological assays for folic acid and vitamin B12 disturbed.

6.2.4.3 Streptomycin

Other ototoxic or nephrotoxic drugs should not be administered to patients receiving streptomycin. These include other aminoglycoside antibiotics, amphotericin B, cephalosporins, ethacrynic acid, cyclosporin, cisplatin, frusemide and vancomycin. Streptomycin may potentiate the effect of neuromuscular blocking agents administrated during anaesthesia.
7. Management of tuberculosis in special situations

7.1 Tuberculosis in children

7.1.1. Pulmonary tuberculosis

• *Diagnosis* in children is usually difficult to make. Most children with pulmonary tuberculosis are sputum direct smear-negative, therefore a high index of suspicion is needed to make the diagnosis.

• Features indicative of tuberculosis are:

  (i) Recent contact with a person (usually adult) with active tuberculosis. This constitutes one of the strongest evidence of tuberculosis in a child who has symptoms and x-ray abnormalities suggestive of tuberculosis.

  (ii) **Symptoms and signs**

      (a) Low grade fever

      (b) Cough

      (c) Weight loss

      (d) Failure to thrive

      (e) Wheezing

      (f) Tachypnoea

      (g) Occasionally frank respiratory distress

      (h) Reduced breath sound

  (iii) Unresolving pneumonia

  (iv) **Positive Mantoux test:**

      A Mantoux test of ≥ 10 mm induration at 72 hours constitutes a positive test.
(v) Chest X-ray:

(a) enlarged hilar lymph nodes ±
    localised obstructive emphysema

(b) Persistent segmental collapse
    consolidation not responding to
    conventional antibiotic.

(c) Pleural effusion

(d) Calcification in lymph nodes, this
    usually develops more than 6
    months after infection

(vi) Gastric lavage for direct smear and
    culture

(vii) Bronchoscopy may be necessary to
    obtain specimens for microbiological
    tests

7.1.2 Anti-tuberculosis chemotherapy in children

• Intensive phase (2 months)

Daily HRZ for 2 months (56 doses). Syrup
preparations should generally be provided on
a fortnightly basis.

• Maintenance phase (4 months)

There are 2 regimens:

(i) Daily RH regimen

This is preferred for younger children
because biweekly regimen may result in
omission of doses by the mother and
the larger doses that need to be given
with biweekly regimen may not be
acceptable to the child.
(ii) Biweekly RH fully supervised regimen

May occasionally be used for older children especially those who live relatively near to the health facility. Ethambutol is best avoided because of the difficulty in detecting visual impairment.

7.1.3 Extra pulmonary tuberculosis

7.1.3.1 Tuberculous meningitis:

The total duration of treatment is at least 12 months. Steroids are usually recommended in the acute stage.

7.1.3.2 Other extra pulmonary tuberculosis:

The regimen and duration of treatment is the same as for pulmonary tuberculosis but may be extended depending on the clinical and/or radiological response.

7.2 Tuberculosis during pregnancy and lactation\textsuperscript{23,24}

Untreated tuberculosis presents a much greater risk to a pregnant woman and her foetus than does the treatment of the disease. Standard treatment using isoniazid, rifampicin, pyrazinamide and ethambutol is used. Doses of anti-tuberculosis drugs given in pregnancy are similar to that in a non-pregnant patient. Streptomycin is best avoided because of the risk of ototoxicity to the foetus. Normal recommended dosages of rifampicin are safe in pregnant patients.

Tuberculosis treatment in lactating mothers is safe as the amount of drug ingested by nursing infant is minimal. If the mother at the time of delivery is smear-positive, the newborn should be separated from the mother at least for a period of two weeks.
Breast-feeding is best avoided during these two weeks and expressed milk should be given to the child. BCG should be given as scheduled and isoniazid prophylaxis should be given for 6 months followed by Mantoux test at the end of 6 months. In the event of absence of scar, BCG vaccination should be repeated. When there is doubt about the presence of active tuberculosis, the child should be treated.

Congenital tuberculosis, although rare should be suspected if an infant born to a tuberculous mother fails to thrive, has non-specific symptoms such as fever, respiratory distress, poor feeding and vomiting, or has suggestive signs such as hepatosplenomegaly.

7.3 Tuberculosis treatment for women taking the oral contraceptive pill

Rifampicin interacts with the oral contraceptive pill, with a risk of decreased protective efficacy against pregnancy. A woman who usually takes the oral contraceptive pill may choose between an oral contraceptive pill containing a higher dose of oestrogen (50mcg) or use another form of contraception after consultation with a doctor.

7.4 Tuberculosis in patients with liver impairment

The patients with no evidence of chronic liver disease (e.g. hepatitis virus carrier, past history of acute hepatitis and alcoholics) can receive the usual short-course chemotherapy regimens but therapy should be modified in patients with established chronic liver disease and acute hepatitis. These cases are best referred to specialists for management.

7.4.1 Established chronic liver disease

The following regimens are recommended:

(i) 2SHRE/7H^2R^2
(ii) 2SHE/10HE
(iii) 2SH/12S^2H^2
7.4.2 Acute hepatitis (e.g. acute viral hepatitis)

It is a rare eventuality that a patient has tuberculosis and also at the same time acute hepatitis unrelated to tuberculosis or anti-tuberculosis treatment. Clinical judgement is necessary. In some cases it is possible to defer tuberculosis treatment until the acute hepatitis has resolved. In other cases when it is necessary to treat tuberculosis during acute hepatitis, the safest regimen is 3SE/6HR.

7.5 Tuberculosis in patients with renal impairment

Isoniazid, rifampicin and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolised into non-toxic compounds. These drugs can, therefore, be given in normal dosage to patients with renal failure. Streptomycin and ethambutol are excreted by kidney. Where facilities are available to monitor renal function closely it may be possible to give streptomycin and ethambutol in reduced doses. The safest regimen to be administered in patients with renal failure is 2HRZ/6HR.

7.6 Extra pulmonary tuberculosis

The regimen of treatment is similar as for pulmonary tuberculosis but the duration may be extended and it varies from 6 months to 12 months or longer depending on the clinical response of the individual patient; for example in tuberculosis meningitis, it is advisable to treat the patient for at least 12 months.

Steroids should be given in tuberculous meningitis, genitourinary tract tuberculosis and may also be considered in miliary tuberculosis.

7.7 Tuberculosis in patients with HIV infection.

Recommended treatment regimens for patients who have tuberculosis with HIV infections (The recommendations are based on those of the CDC, Davidson and The American Thoracic Society-modified)
<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial therapy</strong></td>
<td>Isoniazid, rifampicin, pyrazinamide daily</td>
</tr>
<tr>
<td>• No suspicion of drug resistance</td>
<td></td>
</tr>
<tr>
<td>• Possible drug resistance</td>
<td>Isoniazid, rifampicin, pyrazinamide, Etambutol daily</td>
</tr>
<tr>
<td><strong>Long-term therapy</strong></td>
<td></td>
</tr>
<tr>
<td>• Drug-susceptible organisms</td>
<td>Isoniazid, rifampicin, pyrazinamide for 2 months daily followed by isoniazid, rifampicin for 7 months biweekly or for 6 months after cultures are negative, whichever is longer. Avoid protease inhibitor if regimen contains rifampicin.</td>
</tr>
<tr>
<td>• Isoniazid resistance or intolerance</td>
<td>Rifampicin, ethambutol and Pyrazinamide daily for 2 months followed by rifampicin and ethambutol daily for 12-16 months or 12 months after cultures are negative, whichever is longer. Isoniazid, pyrazinamide, ethambutol</td>
</tr>
<tr>
<td>• Rifampicin resistance or intolerance</td>
<td>Daily for 18 months to 24 months, or for 12 months after cultures are negative whichever is longer.</td>
</tr>
</tbody>
</table>
8. Fixed-dose combinations (FDC) of anti-tuberculosis drugs

Fixed-dose combinations (FDC)

Fixed-dose combination (FDC) tablets incorporate two or more drugs within the same tablets (Isoniazid, Rifampicin and Pyrazinamide). The following preparations are available in the private sector:

1. Rifinah / Rimactazid / Rifamate (combinations of rifampicin and isoniazid).
2. Rifater (combination of rifampicin, isoniazid and pyrazinamide).
3. Myrin (ethambutol, rifampicin and isoniazid).
4. Myrin P (ethambutol, rifampicin, isoniazid and pyrazinamide).

8.1 Advantages

(i) reduced risk of emergence of drug-resistant organisms
(ii) an effective regimen is more likely to be prescribed
(iii) opportunity for inadvertent medication errors is decreased
(iv) many of the logistic problems which cause shortage of individual drugs are limited
(v) promotes patient compliance
(vi) decreased usage of rifampicin for other infections
8.2 Disadvantages

(i) Bioavailability: WHO and IUATLD recommend the use of only FDCs for which *in vivo* studies have demonstrated satisfactory bioavailability of rifampicin.

(ii) Cost: Prices may fall as use becomes more widespread.

(iii) May be necessary to adjust the dosage; programmes using FDCs still require limited amounts of single drugs.
9. DOTS- Directly Observed Treatment, Short-course

DOTS

The acronym stands for Directly Observed Treatment, Short-course. The DOTS strategy comprises the following five elements for its success:

1. Government commitment to a National Tuberculosis Control Programme.

2. Case detection through sputum smear microscopy examination of tuberculosis suspects in general health services.

3. A standardised short-course tuberculosis treatment regimen of six months under direct observation by a trained supervisor to ensure the patient takes every dose of medication.

4. A regular, uninterrupted supply of quality anti-tuberculosis drugs.

5. A monitoring and reporting system to evaluate treatment outcome for each and every patient with proper documentation

9.1 Advantages of DOTS

(i) DOTS can produce cure rates of up to 95% even in the poorest countries.

(ii) This strategy can be integrated successfully within existing primary health care services to achieve widespread coverage.

(iii) Case detection by sputum microscopy is cheap, simple and reliable.

(iv) Trained health care workers or even community volunteers can supervise the treatment.
(v) DOTS does not require hospitalisation or isolation; patients can remain with their families and return to work in a few days.

(vi) DOTS helps to prevent drug resistance which is often fatal and up to 100 times more expensive to treat than drug susceptible cases\textsuperscript{16}

(vii) The DOTS recording and monitoring system follows each patient through the entire course of treatment to ensure a cure.

(viii) DOTS is a sound economic investment for any government. Each healthy year of life brought about by using DOTS costs as little as US $1\textsuperscript{16}.

9.2 DOTS in Malaysia

Malaysia is committed to adopting the DOTS strategy. All drugs should be administered under supervision i.e. directly observed by health personnel or trained person. Each dose of medication taken by the patient under supervision should be recorded. Supervision of treatment need not necessarily be confined to health care facilities.
10. Defaulter tracing and retrieval

10.1 Definition of 'defaulter'

A patient who has missed more than 25% of the treatment doses in one month ie., more than 6 doses of daily treatment or more than 2 doses of biweekly treatment.

10.1.1 Steps to be taken by treatment centre when patient misses a dose:

1. Send first reminder letter or phone call on the same day

2. Second reminder letter or phone call if patient does not turn up the next day

3. If patient does not turn up on 3rd day, home visit must be done to retrieve patient.

All treatment centres must report tuberculosis patients who default treatment for 1 week to the nearest district health office.

10.2 Contact management

All persons staying in the same house or have been in close contact with the presenting index case should be investigated (see appendix 1 and 2)
11. Outcome analysis

Outcome analysis

- Form 1a to be completed for every patient on initiation of treatment.
- Form 1b to be completed at the end of treatment / disposal

Analysis of form 1a and form 1b is to be done for every new smear-positive case after 1 year of follow-up. Cure rate, treatment completion rate, treatment failure rate, treatment interrupted rate and death rate during treatment should be calculated based on form 1a and form 1b.

11.1 Cure

Patient who is smear-negative at, or one month prior to, the completion of treatment and on at least one previous occasion

11.2 Treatment completed

Patient who has completed treatment but without proof of cure

11.3 Treatment failure

Patient who remains or becomes again smear-positive at five months or later during treatment

11.4 Died

Patient who dies for any reason during the course of treatment

11.5 Treatment interrupted

Patient whose treatment was interrupted for 2 months or more
12. Management of resistant tuberculosis

12.1 Definitions

(i) Drug-resistant tuberculosis
This is a case of tuberculosis (usually pulmonary) excreting bacilli resistant to one or more anti-tuberculosis drugs.

(ii) Multidrug-resistant tuberculosis
This is a case of tuberculosis which is resistant to at least isoniazid and rifampicin.

12.2 Management of resistant tuberculosis

12.2.1 Pharmacological treatment:

The most important line of management is prevention by initiating treatment of all cases of confirmed tuberculosis on effective drug regimen followed by directly observed treatment follow-up. All cases of resistant tuberculosis should be referred to and the treatment should be initiated by trained physicians.

12.2.1.1 Second line drugs

2nd line anti-tuberculosis drugs

<table>
<thead>
<tr>
<th>2nd line drug</th>
<th>Recommended dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin/kanamycin</td>
<td>15mg/kg/day 5x/week</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 - 600mg/day</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>750 - 1500mg/day</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>15mg/kg/day</td>
</tr>
<tr>
<td>Enviomycin</td>
<td>15mg/kg/day 5x/week</td>
</tr>
<tr>
<td>Capreomycin*</td>
<td>15mg/kg/day 5x/week</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500mg bd</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>500 mg daily</td>
</tr>
<tr>
<td>Para amino salicylic acid</td>
<td>12 - 16gm/day</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>15 - 20mg/kg/day</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>100 - 300mg/day</td>
</tr>
<tr>
<td>Thiacetazone*</td>
<td>150mg/day</td>
</tr>
</tbody>
</table>

* Not used in Malaysia.
Basic principles

- Assume that all patient with apparent drug resistant tuberculosis will have bacilli resistant to isoniazid.
- It is advisable to manage patient with MDR TB as in-patient until sputum conversion is achieved.
- In designing a regimen, do not aim to keep drugs in reserve.
- Prescribe drugs which the patient has not had previously.
- The initial regimen should consist of at least three drugs, preferably four or five, to which the bacilli are likely to be fully sensitive.
- Among these drugs, it is desirable to use in combination an injectable aminoglycoside and pyrazinamide, even if previously used because resistance is usually unlikely. This combination has good bactericidal activity.
- On sputum conversion to negative, one or more drugs may be withdrawn, preferably a weaker drug which is causing side-effects.
- The treatment with the weaker regimen should be continued for at least 18 months after sputum conversion to prevent relapse.
- In any regimen chosen especially when weaker drugs are used the treatment should be given daily and should be directly observed. It is also mandatory to monitor bacteriological results i.e. smear and culture monthly from the second month until the sixth month, and then quarterly till the end of treatment.

12.2.2 Surgical Intervention

Surgery should be considered for a patient with bacilli resistant not responding to medical treatment. Unfortunately many such patients will have too extensive disease and/or too poor lung function for surgery. Operation should be done when the bacillary population is likely
to be lowest. After surgery the same drug regimen should be continued for at least 18 months.

12.3 BCG vaccination in Malaysia

BCG vaccination is given to all newborns. Vaccination for children with no scar is done at primary school entry or earlier.

12.4 Tuberculosis in Foreign workers

All foreign workers found to have CXR abnormalities should be fully investigated for tuberculosis and if found to have active tuberculosis, should receive treatment (including those in detention camps) until further action by the relevant authorities.

12.5 Chemoprophylaxis

(i) Chemoprophylaxis is indicated in HIV positive patients who have Mantoux reading of $\geq 5$mm regardless of age or prior skin testing results. Chemoprophylaxis with isoniazid should also be considered for anergic HIV infected patients who are known contacts of persons with infectious tuberculosis. They should be evaluated carefully for active tuberculosis before preventive therapy is started. The recommended duration of chemoprophylaxis with isoniazid in HIV infected patients is 12 months. Compliance to chemotherapy with isoniazid should be considered carefully when chemoprophylaxis is to be instituted. In the event of suspected isoniazid resistance, a combination of two drugs eg., isoniazid and rifampicin, may be required for 6 months.

(ii) Asymptomatic children under 5 years old who are contacts of infectious tuberculosis cases, with Mantoux reading $\geq 10$mm should receive isoniazid 5mg/kg once daily for a minimum of 6 months.
13. Prevention of tuberculosis among health care workers (HCW)

Tuberculosis is a very infectious disease, spread by droplets from a sputum positive source via coughing, sneezing, talking and singing. Tuberculosis organisms may remain airborne after being coughed out. The probability that a person who is exposed to *M. tuberculosis* will become infected depends primarily on the concentration of the infectious droplet nuclei in the air and the duration of exposure.

The risk of spread of tuberculosis from a given source case is related to several factors; organism load, ventilation of working environment, protective measures taken by the HCW and duration of exposure to the organism. The size of the risk varies according to the type of health care setting, the prevalence of tuberculosis in the community, the patient population served, the area of the health-care facility in which the HCW works and the effectiveness of tuberculosis infection control interventions.

The risk of infection is higher in areas where patients with tuberculosis are provided care before diagnosis and initiation of tuberculosis treatment or where diagnostic or treatment procedures that stimulate coughing are performed. In hospitals where there were more than 200 sputum smear positive admissions annually, infection occurred in 1 to 10 percent of workers each year\(^\text{18}\). The prevalence of infection is directly proportional to the duration of employment in the hospital.

There is no permissible level of exposure to tubercle bacilli\(^\text{19}\). Studies in guinea pigs showed that inhalation of a single droplet nucleus containing no more than three tubercle bacilli can result in conversion on tuberculin testing and the development of macroscopic granuloma\(^\text{20}\).
The transmission of tuberculosis to HCWs is dependent on the following factors:

1. the number of patients with active tuberculosis in contact with the HCW,
2. the infectiousness of the index case,
3. the ventilation rate of the worker,
4. the duration of exposure, and
5. the air-exchange rate in the interior space.

High index of suspicion for tuberculosis with prompt diagnosis and treatment can limit its spread to HCWs. All HCWs and supportive staff should be periodically trained to recognise the symptoms and signs of tuberculosis and to initiate protection protocols.

### 13.1 TB infection control

Effective infection control efforts are essential in preventing nosocomial transmission of tuberculosis. A hierarchy of control measures is recommended to prevent tuberculosis transmission in health care facilities.

1. **Administrative controls:** Administration controls are most important in preventing nosocomial transmission of tuberculosis. This measure is primarily intended to reduce the risk for exposing the uninfected HCW to tuberculosis. Measures include developing and implementing effective protocols to ensure rapid identification, isolation and treatment. Effective work practices among HCW should be implemented and there should be education, training and counseling about tuberculosis. Finally HCWs should be screened for tuberculosis.

2. **Engineering controls:** This measure will prevent the spread and reduce the concentration of infectious droplet nuclei. These controls include local exhaust ventilation, unidirectional airflow, general ventilation and air cleaning via filtration or ultraviolet germicidal irradiation (UVGI). Biological safety cabinets Class II should be used by laboratory personnel handling infectious material.
3. **Personal Respirator Protection**: Appropriate respirator masks should be worn by HCWs when performing high risk procedures such as cough induction and bronchoscopy.

### 13.2 Surveillance of HCWs for latent tuberculosis

All HCWs should have chest x-ray upon employment. Those working in high risk areas should have chest x-ray at intervals of once every 2 years. Any worker who develops symptoms of tuberculosis should be evaluated promptly. HCWs with active tuberculosis should be treated promptly and be given leave from duties until sputum AFBs are negative and the HCW has completed treatment.

The risk of nosocomial transmission of tuberculosis varies considerably among and within health care setting. The complete elimination of risk among HCWs is an unrealistic goal. A more rational objective is the reduction of risk to a level similar to that in the general population. There is evidence that HCWs working in high risk areas such as chest clinic, wards treating active tuberculosis and laboratory staff are among the risk group. Several control measures as mentioned earlier need to be implemented to reduce transmission of the bacilli to the HCWs.

**NOTE**: For further information please refer guidelines.
References


3. Barnes PF. Rapid Diagnostic Test for Tuberculosis. AM J Respir Crit Care Med. 1997; V 155: 1497 -1498


18. CDC Guidelines for the preventing the transmission of mycobacterium tuberculosis in Health Care facilities., 1994, MMWR 43 (RR13); 1-132


21. Tuberculosis among Health Care Workers. NEJM vol 332, no. 2; 92-98


Flow chart for contact investigation (Adults)

Tuberculosis Contacts

Chest X-ray

Normal

Abnormal

Symptomatic

Register for investigations at Chest Clinic

Full Investigations

D/S & Culture + ve

NOTIFY, REGISTER TREAT

D/S & or Culture - ve

Treat if symptomatic or review at 3 months, 6 months and one year if asymptomatic

Asymptomatic review at 3, 6 months & 1 year
Flow Chart for Management of Tuberculosis contacts (Children)

CHILD (Contact)

Mantoux Test

>10mm

CXR

normal

Asymptomatic

Symptoms suggestive of TB

<5yrs old

Follow up

>5yrs old

Chemo-prophylaxis

abnormal

Symptomatic

CXR

normal

Investigate further

Treat as TB

abnormal

Treat high risk

Asymptomatic

Check BCG

No scar

2 scar

Follow-up